REMARKS

Claims 1-13 and 16-22 are pending and presented for examination. Applicants have amended claim 1 to refer to claim 16. Applicants have amended claim 6 to refer to claim 10; to delete unnecessary words; and to insert the word "and" between steps c) and d). Applicants have amended claim 10 to clarify that the nucleotide sequences of the primers consist of the sequences selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO: 12. Applicants have made this amendment to correct what the restriction requirement alleged to be an ambiguity in the scope of claim 1. Specifically, the restriction requirement stated that: "Claim 10 does not specify the primers of SEQ ID NO 1-12 consist of sequences of SEQ ID NO 1-12" (p. 3). Without agreeing to the examiner's reading of claim 10, applicants have amended the claim to clarify its scope.

Applicants submit that these amendments add no new matter to the application, which discloses primers whose nucleotide sequences consist of the sequences selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO:12.

Unity of Invention

Applicants request the withdrawal of the restriction requirement set forth in the paper of September 3, 2009.

The restriction requirement obligated Applicants to elect either Group I, claims 1-9; or Group II, claims 10-13 and 16-22. Applicants elect Group I, with traverse.

As a threshold matter, Applicants believe claim 10 to have been misunderstood. Specifically, claim 10 required primers selected from the group consisting of SEQ ID NO: 1 to SEQ ID NO:12. The restriction requirement chose to interpret the claim as having primers *comprising* SEQ ID NO: 1 to SEQ ID NO: 12. The allegation of lack of unity of invention appears to rely, in whole or in part, on this misunderstanding. Applicants have amended the claim to expressly address and clarify this misunderstanding (without altering what Applicants believe to be the scope of the claim). As the restriction requirement relied on a claim

interpretation that cannot be reconciled with the amended claim, Applicants request that the restriction be reconsidered and withdrawn.

The requirement was also inaccurately based on a conclusion that "the components of kit of claim 10 was taught to one of ordinary skill by prior art" (p. 5).

The applied references do not permit such a conclusion. The restriction requirement correctly notes that Kobler and Fieldhouse (WO 02/059355) teach nucleotide tag sequences, a subset of which are incorporated into primers of claim 10 (p.4). Humeny *et al.* (2001) Clinical Biochemistry 34:531-6 allegedly teaches the use of allele specific extension primers to detect mutations known to be associated with thrombosis (Restriction requirement, p. 3). Venter *et al.* (U.S. Patent No. 6,812,339) allegedly teaches a sequence that is 601 bp long, a portion of which apparently corresponds to a portion of the present SEQ ID NO:10.

None of the applied references teaches any of the primers required in claim 10. As such, it cannot be said that "the components of the kit" were taught in the prior art. Rather, each of the components of the kit are novel and inventive. Applicants have succeeded in designing novel ***tagged*** allele specific extension primers combining 3'-end hybridizing portions with 5'-end tag portions. These ***tagged*** primers, and combinations thereof, ***simultaneously*** meet the stringent requirements of multiplex detection from multiplex amplification reactions, generally from genomic DNA, to provide the requisite ***sensitivity*** and ***specificity*** to simultaneously identify with precision an individual's genotype at a ***plurality of loci*** associated with thrombosis.

Importantly, the sensitivity and specificity do not flow solely from the sequence of the 3'-end hybridizing portion. Rather, they are always a function of the sequence of the entire primer, including the 3' and 5' portions. For example, in a poorly designed primer:

- The sequence of the 5'-end tag portion could itself hybridize inappropriately to genomic DNA;
- A portion of the primer overlapping the 5'-end tag portion and the 3'-end hybridizing portion could hybridize inappropriately to genomic DNA;

- The 5'-end tag portion could form inappropriate secondary or tertiary intramolecular or intermolecular structures with the 3'-end hybridizing portion, interfering with the function of either or both ends.

The kits of claim 10 avoid these pitfalls and achieve sensitivity and specificity through the careful selection of 3'-end hybridizing portions, ***each combined with an individually selected*** 5'-end tag portion that permits interaction with an anti-tag ***without*** inappropriate interactions with the 3'-end hybridizing portion or with the genomic DNA, either of which could introduce false negative or false positive test results. The sequences of the tagged primers used in the invention of claim 10 are thus not merely novel. They are non-obvious, as they provide important advantages beyond those provided by any one of the applied references.

Applicants therefore respectfully request that the requirement based on an alleged lack of unity of invention be reconsidered and withdrawn.

Applicants have also amended claims 1 and 6 to refer to composition and kit claims 16 and 10, respectfully. Applicants look forward to the rejoinder of the method claims once the composition and kit claims have been deemed allowable, even if the restriction requirement were otherwise maintained until that time.

Restriction subgroup

Applicants have also been required to elect 2 tagged allele specific primers and 2 pairs of amplification primers for prosecution on the merits. Applicants request that this requirement be reconsidered and withdrawn. Applicants submit that no restriction can be proper in an international application that has entered the U.S. national phase in accordance with 35 U.S.C. § 371 if the claimed subject matter relates to a single general inventive concept. See PCT Rule 13.1. The restriction requirement presents no arguments that this "subgroup" lacks a single general inventive concept. Applicants submit that no prior art teaches or suggests tagged primers with a 3'-end hybridizing portion and a 5'-end tag portion that simultaneously provide the advantages in multiplex thrombosis genotype detection offered by the present invention. In the

presence of a single general inventive concept, Applicants submit that the restriction is improper and should be withdrawn.

Applicants elect, with traverse, SEQ ID NO: 2 and SEQ ID NO:4 as the tagged allele specific primers and SEQ ID NOS: 13 and 14 and SEQ ID NOS: 15 and 16 as the 2 pairs of amplification primers. Applicants submit that all pending claims are readable on the elected sequences.

The Examiner is invited to call the undersigned with any questions or comments if the Examiner believes a telephone conversation would be helpful in expediting the prosecution of the instant application.

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Respectfully submitted,

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